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A General Palladium-Catalyzed Carbonylative Synthesis of 2-Alkylbenzoxazinones from 2-Bromoanilines and Acid Anhydrides

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Benzoxazinones represent a class of annulated nitrogen heterocycles that are of interest in organic synthesis due to their various biological activities.[1] Among the different methodologies developed for their preparation,[2] the cyclization of anthranilic acid, *N*-acylanthranilic acid or isotonic anhydride are the most accepted.[3] Although alternative methodologies are known,[4] the availability of substrates and the required reaction conditions have limited their application so far.

Palladium-catalyzed carbonylation reactions allow for a general synthesis of many kinds of benzoic acid derivatives from easily available starting materials, such as (hetero)aryl halides and inexpensive carbon monoxide.[5] Combining this carbonylative process with a subsequent intramolecular cyclization reaction would allow efficient access to different heterocycles;[6] however, in this respect, few palladium-catalyzed carbonylative syntheses of benzoxazinones are known.[7] The first example, which involves a stoichiometric thallation and subsequent carbonylation of *N*-acetylaniline, was reported by Larock and Fellows.[7a] Later, Cacchi and co-workers published a general method for the carbonylative coupling of 2-iodoanilines with unsaturated halides or triflates.[7b] In addition, similar carbonylative coupling reactions of 2-iodoanilines with acid chlorides were developed by Alper and Petricci and their co-workers.[7c,d] Recently, an interesting method for the palladium-catalyzed carbonylative C–H activation of benzanilides and aryl urea derivatives was developed independently by Yu et al.[7f] and Loyd-Jones, Booker-Milburn et al.[7e] More recently, our group reported an efficient palladium-catalyzed carbonylative coupling of aryl bromides with 2-bromoanilines to 2-arylbenzoxazinones in good yields;[7h] however, we failed in the preparation of 2-alkyl substituted benzoxazinone derivatives. Based on our ongoing interest in palladium-catalyzed carbonylation reactions,[8] we herein wish to present a new carbonylation procedure that allows for a general synthesis of 2-alkylbenzoxazinones starting from easy available 2-bromoanilines and acid anhydrides.

Initial experiments were carried out by using the carbonylation of 2-bromoaniline and Ac_2O as a model reaction. We have recently shown that the Pd/$BuPAd_2$ catalyst system is well suited for different carbonylations.[9] Hence, we initially used this catalyst system at 100 °C in the presence of NEt_3 and various solvents for our investigations (Table 1, entries 1–6). Toluene, as a non-polar solvent, gave better yields than polar solvents, and 73% of the desired product was produced when this solvent was used (Table 1, entry 1). Thus we used toluene as the solvent to test the influence of various ligands. The use of PPh_3 resulted in a lower yield, and no product was formed with $P(tolyl)_3$ as the ligand (Table 1, entries 7 and 8). The bidentate phosphine ligands that were tested show comparable results to $BuPAd_2$, and gave 62–71% yield of the desired products (Table 1, entries 9–12). The reactions were also carried out with different bases; an improved yield was obtained by using DiPEA as the base, but none of the desired product was formed with the use of inorganic bases (Table 1, entries 13–18). The effect of different palladium salts was also tested (Table 1, entries 19–23). 2-Methylbenzoxazinone was produced in 84% yield by applying K_2PdCl_4 as the catalyst precursor (Table 1, entry 23). By combining the most effective base (DiPEA) and palladium salt (K_2PdCl_4), the yield of desired product was further improved to 88% (Table 1, entry 24). With the use of 1 mol% of the catalyst, the yield of our desired product decreased to 47%, and *N*-(2-bromophenyl)acetamide was formed as a byproduct in 50% yield (Table 1, entry 25). To our delight, a 95% yield of 2-methylbenzoxazinone was obtained from the reaction with 1.5 equivalents of Ac_2O, which could even be carried out under 2 bar of CO without a change in the yield (Table 1, entries 26 and 27).

With the best conditions in hand, we tested the generality of this methodology. Methyl-, fluoro- and chloro-substituted 2-bromoanilines reacted successfully with Ac_2O and gave the desired products in isolated yields of 83–94% (Table 2, entries 2–7). 7-Acetyl-2-methyl-4*H*-benzoxazin-4-one was obtained in 84% yield from the corresponding 2-bromoaniline derivative (Table 2, entry 8). Pyridine was used as a representative example of a heterocycle, and its bromoamino derivative was transformed into the corresponding benzoxazinone in 89% yield (Table 2, entry 9).

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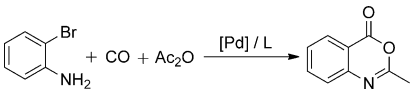
Table 1. Palladium-catalyzed carbonylative coupling of 2-bromoaniline.[a]



Entry	[Pd]	Ligand	Solvent	Base	Yield [%][b]	Entry	[Pd]	Ligand	Solvent	Base	Yield [%][b]
1	$Pd(OAc)_2$	$BuPAd_2$	toluene	NEt_3	73	15	$Pd(OAc)_2$	$BuPAd_2$	toluene	DBU	62
2	$Pd(OAc)_2$	$BuPAd_2$	dioxane	NEt_3	64	16	$Pd(OAc)_2$	$BuPAd_2$	toluene	NBu_3	79
3	$Pd(OAc)_2$	$BuPAd_2$	DMF	NEt_3	39	17	$Pd(OAc)_2$	$BuPAd_2$	toluene	K_2CO_3	0
4	$Pd(OAc)_2$	$BuPAd_2$	DMSO	NEt_3	39	18	$Pd(OAc)_2$	$BuPAd_2$	toluene	K_3PO_4	0
5	$Pd(OAc)_2$	$BuPAd_2$	DMAc	NEt_3	49	19	$PdCl_2$	$BuPAd_2$	toluene	NEt_3	73
6	$Pd(OAc)_2$	$BuPAd_2$	NMP	NEt_3	52	20	$PdBr_2$	$BuPAd_2$	toluene	NEt_3	78
7	$Pd(OAc)_2$	PPh_3	toluene	NEt_3	52	21	$Pd(TFA)_2$	$BuPAd_2$	toluene	NEt_3	65
8	$Pd(OAc)_2$	$P(o\text{-tolyl})_3$	toluene	NEt_3	0	22	K_2PdBr_4	$BuPAd_2$	toluene	NEt_3	79
9	$Pd(OAc)_2$	DPPP	toluene	NEt_3	62	23	K_2PdCl_4	$BuPAd_2$	toluene	NEt_3	84
10	$Pd(OAc)_2$	DPEphos	toluene	NEt_3	71	24	K_2PdCl_4	$BuPAd_2$	toluene	DiPEA	88
11	$Pd(OAc)_2$	DPPF	toluene	NEt_3	62	25	K_2PdCl_4	$BuPAd_2$	toluene	DiPEA	47[c]
12	$Pd(OAc)_2$	DPPB	toluene	NEt_3	71	26	K_2PdCl_4	$BuPAd_2$	toluene	DiPEA	95[d]
13	$Pd(OAc)_2$	$BuPAd_2$	toluene	DiPEA	83	27	K_2PdCl_4	$BuPAd_2$	toluene	DiPEA	96[e]
14	$Pd(OAc)_2$	$BuPAd_2$	toluene	TMEDA	73						

[a] [Pd] (2 mol%), ligand (4 mol%), solvent (2 mL), base (2.2 mmol), 2-bromoaniline (1 mmol), Ac_2O (1 mmol), CO (5 bar), 100°C, 16 h. [b] Yield was determined by GC using hexadecane as the internal standard. [c] K_2PdCl_4 (1 mol%), $BuPAd_2$ (2 mol%). [d] Ac_2O (1.5 mmol). [e] CO (2 bar), Ac_2O (1.5 mmol). $BuPAd_2$ = *n*-butyldiadamantylphosphine; DMAc = *N*,*N*-dimethylacetamide; NMP = *N*-methyl-2-pyrrolidone; DPPP = 1,3-bis(diphenylphosphino)propane; DPEphos = bis[(2-diphenylphosphino)phenyl] ether; DPPF = 1,1′-bis(diphenylphosphino)ferrocene; DPPB = 1,4-bis(diphenylphosphino)-butane; DiPEA = *N*,*N*-diisopropylethylamine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TFA = trifluoroacetic acid.

We then choose 2-bromoaniline as a standard substrate to perform the test reactions with different acid anhydrides (Table 3). Various substituents were tolerated under our standard conditions and gave good product yields. Interestingly, 2-trifluoromethyl-substituted benzoxazinone was produced in good yield from trifluoroacetic anhydride and 2-bromoaniline (Table 3, entry 9). 2-Phenylbenzoxazinone was produced in 86% yield from the reaction of 2-bromoaniline with benzoic anhydride (Table 3, entry 10).

In conclusion, an efficient and general procedure for the production of 2-alkylbenzoxazinones has been developed. By starting from readily available 2-bromoanilines, inexpensive acid anhydrides and CO, various benzoxazinones were isolated in good to excellent yields.

Experimental Section

General procedure: K_2PdCl_4 (2 mol%) and $BuPAd_2$ (4 mol%) were transferred into a vial (4 mL reaction volume) that was equipped with a septum, a small cannula and a stirring bar. After the vial was purged with argon, 2-bromoaniline (1 mmol), an acid anhydride (1.5 mmol), toluene (2 mL), DiPEA (2.2 mmol) and hexadecane (0.1 mL, internal GC standard) were injected into the vial by syringe. The vial was then placed in an alloy plate, which was transferred into an autoclave (300 mL; 4560 series from Parr Instruments) under an argon atmosphere. After flushing the autoclave three times with CO, the pressure was adjusted to 2 bar, and the reaction was performed for 16 h at 100°C. After the reaction was complete, the autoclave was cooled to room temperature and the pressure was carefully released. Water (6 mL) was added to the reaction mixture, and the solution was extracted 3–5 times with ethyl acetate (2–3 mL). The combined organic extracts were evaporated in vacuo with adsorption onto silica gel, and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (7:3) as the eluents.

Acknowledgements

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Keywords: bromoanilines · benzoxazinones · carbonylation · heterocycles · palladium

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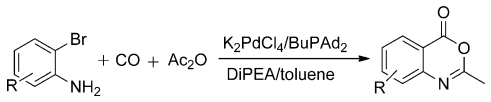
Table 2. Palladium-catalyzed carbonylative coupling of 2-bromoanilines with Ac_2O.[a]



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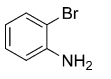
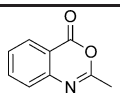
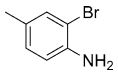
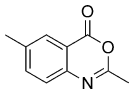
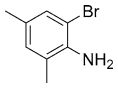
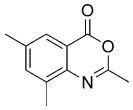
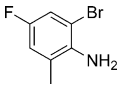
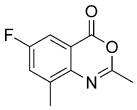
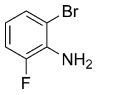
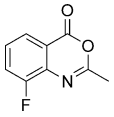
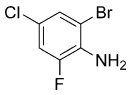
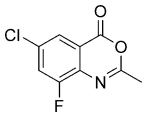
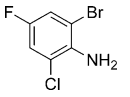
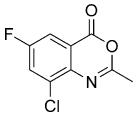
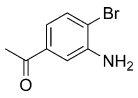
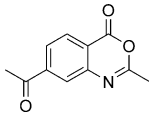
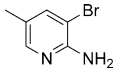
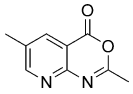
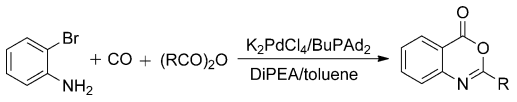
1			90
2			91
3			94
4			89
5			83
6			89
7			88
8			84
9			89

[a] K_2PdCl_4 (2 mol%), $BuPAd_2$ (4 mol%), toluene (2 mL), DiPEA (2.2 mmol), 2-bromoaniline (1 mmol), Ac_2O (1.5 mmol), CO (2 bar), 100°C, 16 h. [b] Isolated yields.

Table 3. Palladium-catalyzed carbonylative coupling of 2-bromoaniline with acid anhydrides.[a]



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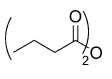
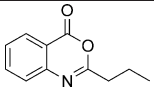
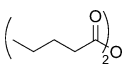
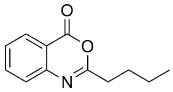
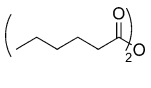
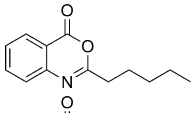
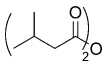
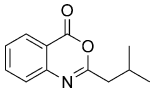
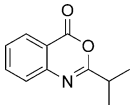
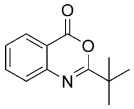
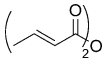
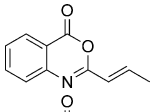
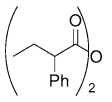
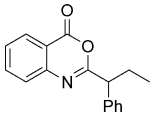
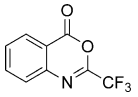
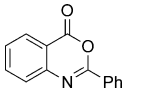
1			85
2			67
3			79
4			71
5			80
6			55
7			88
8			46
9	$(CF_3CO)_2O$		74
10	$(PhCO)_2O$		86

[a] K_2PdCl_4 (2 mol%), $BuPAd_2$ (4 mol%), toluene (2 mL), DiPEA (2.2 mmol), 2-bromoaniline (1 mmol), acid anhydride (1.5 mmol), CO (2 bar), 100°C, 16 h. [b] Isolated yields.

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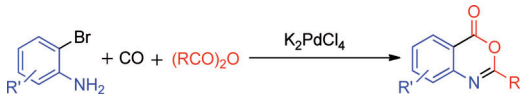

(C), its (O)K! An efficient palladium-catalyzed carbonylative synthesis of 2-alkylbenzoxazinones has been developed (see scheme). By starting from 2-bromoanilines and acid anhydrides, the corresponding products were isolated in good yields.

Carbonylation

X.-F. Wu, H. Neumann, M. Beller** ..... ▮▮▮▮–▮▮▮▮

A General Palladium-Catalyzed Carbonylative Synthesis of 2-Alkylbenzoxazinones from 2-Bromoanilines and Acid Anhydrides